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Previews

TXNIP Links Redox Circuitry to Glucose Control

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Thioredoxin-interacting protein (TXNIP) binds and inhibits the reducing activity of thioredoxin. A new study (Parikh et al., 2007) implicates this redox rheostat as a negative regulator of peripheral glucose metabolism in humans. Investigators combined human physiology, genomic screening, and cell-based genetic studies to highlight TNXIP as a potential culprit in the pathogenesis of type 2 diabetes.

Modern technology has created a favorable climate for the "perfect metabolic storm" that is now raging through Westernized societies as an epidemic of obesity and type 2 diabetes (Zimmet et al., 2001). Topping the list of casualties is glucose homeostasis, a weathered victim of lifestyle habits that promote overeating and inactivity. Normal control of blood glucose depends on exquisite coordination between the insulin-producing pancreatic β cells and insulin-responsive target tissues such as skeletal muscle, liver, and fat. In the context of metabolic disease, these target tissues fail to effectively adjust glucose uptake and metabolism in response to insulin. As a result, the β cell must compensate by amplifying its secretion of the hormone. This insulin-resistant/glucose-intolerant state is universally present in patients with type 2 diabetes, a disease that eventually takes hold when β cell failure results in sustained hyperglycemia.

Relief efforts, in the form of efficacious antidiabetic pharmaceuticals, depend heavily on a deeper understanding of the molecular events that connect energy surplus to glucose intolerance. To this end, Parikh and colleagues (2007) have identified thioredoxin-interacting protein (TXNIP) as a potential diabetogenic signal in human skeletal muscle. TXNIP is a ubiquitous protein inhibitor of thioredoxin, an oxidoreductase that partners with thioredoxin reductase and thioredoxin peroxidase to reduce oxidized proteins and scavenge free radicals (Figure 1A). Their investigation featured a unique translational approach that combined human physiology studies with genome-wide transcriptomics, genetic association testing, and cell-based genetic engineering tools. The initial genomic study involved a screen of 12 healthy subjects to identify skeletal muscle mRNAs whose abundance is altered in response to a euglycemic-hyperinsulinemic clamp. In healthy subjects, expression levels of TXNIP were potently suppressed by insulin and negatively correlated with glucose disposal. By contrast, these relationships were lost in diabetic subjects. Using previously published microarray data, the investigators found that muscle expression of TXNIP was consistently higher in patients with diabetes or prediabetes as compared to those with normal glucose tolerance. TXNIP was not upregulated in muscle of healthy subjects with a family history of disease, and the researchers found no association between diabetes susceptibility and genetic variation at the *TXNIP* locus, suggesting that dysregulation of the gene is an acquired rather than inherited trait.

Because insulin-mediated regulation of TXNIP was absent in insulin receptor knockout mice, the investigators further concluded that suppression of TXNIP requires intact insulin signaling. As a complementary approach, the researchers performed a series of experiments in terminally differentiated human skeletal myocytes and adipocytes. In both systems, administration of insulin suppressed TXNIP mRNA levels, whereas exposure of cells to high glucose caused reciprocal upregulation of the gene. The functional consequence of these changes was then tested by artificial manipulation of TXNIP. Lentivirus-mediated overexpression of TXNIP in 3T3-L1 adipocytes decreased both basal and insulin-stimulated transport of 2-deoxyglucose, a nonmetabolizable glucose analog, whereas silencing of the gene by RNA interference augmented uptake in both myocytes and adipocytes. However, the full implications of these findings cannot yet be fully evaluated since corresponding effects on glucose metabolism, redox state, oxidative stress, and insulin signaling were not reported.

The study showed that TXNIP is reciprocally regulated by insulin and glucose. To explain this seemingly counterintuitive finding, the authors proposed a model in which TXNIP functions as a homeostatic switch that integrates glucose sensing and insulin signaling to control cellular energy status. For example, insulin-mediated suppression of TXNIP might act as a feed-forward signal that enhances glucose disposal in the periphery to facilitate post-meal refueling. Conversely, a surplus of intracellular glucose activates TXNIP, bringing glucose uptake to halt. This negative feedback mechanism might serve as "trip switch" that prevents excessive glucose uptake and metabolism (Figure 1B). Although the report stopped short of offering a biological mechanism to explain the relationship between elevated TXNIP and glucose intolerance, several intriguing possibilities emerge from previous work. TXNIP is also known as vitamin D_3-upregulated protein or thioredoxin-binding protein 2 and inhibits thioredoxin function by binding to its

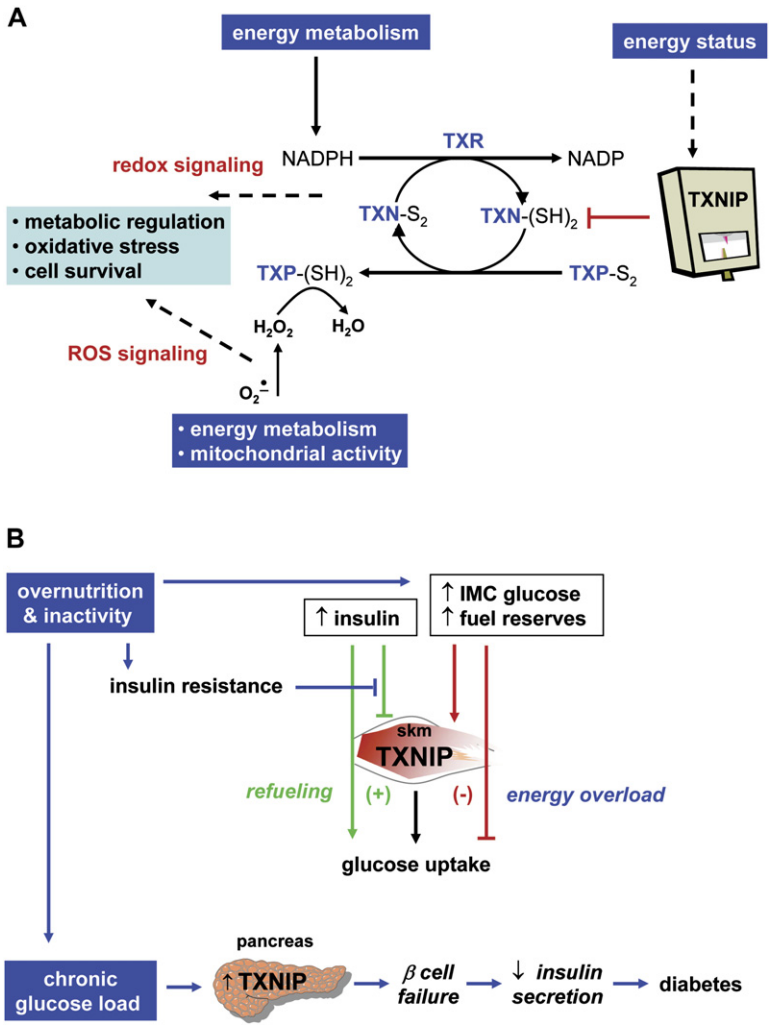

Figure 1. Models of TXNIP Action

(A) Role of TXNIP in the thioredoxin system. Thioredoxin (TXN) reduces oxidized cysteine residues (protein-S_2) on cellular proteins. Reduced TXN (TXN-$(SH)_2$) is regenerated via the action of thioredoxin reductase (TXR) at the expenditure of NADPH. When TXN reduces the oxidized form of thioredoxin peroxidase (TXP), the reduced enzyme (TXP-$(SH)_2$) is available to scavenge reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) and the superoxide anion ($O_2^{\bullet -}$). TXNIP binds and inhibits the reduced form of TXN, thereby functioning as a rheostat that modulates both redox status and ROS-mediated signaling to regulate metabolism and other cellular processes. (Dashed arrows indicate unknown mechanisms.)

(B) Proposed role of TXNIP in type 2 diabetes. Insulin-mediated suppression of skeletal muscle (skm) TXNIP serves as a feed-forward signal (+) that enhances glucose uptake and facilitates post-meal refueling. A surplus of intramyocellular (IMC) glucose activates TXNIP, which exerts negative feedback (−) to discourage import of additional fuel. The energy burden of overnutrition and inactivity (blue lines) leads to constitutively high levels of TXNIP in skeletal muscle, which is further exacerbated by peripheral insulin resistance. This vicious cycle imposes a chronic glucose load on the pancreas, triggering TXNIP-mediated β cell failure and overt diabetes.

redox-active cysteine residues (Nishiyama et al., 1999). Growing evidence positions the thioredoxin system at a nodal point linking pathways of redox regulation, antioxidant defense, energy metabolism, and cell growth and survival. TXNIP is elevated in the vasculature and pancreas of diabetic animals, suggesting a broad role in diabetes complications (World et al., 2006). Notably, TXNIP is also glucose inducible in pancreatic β cells, possibly mediating glucotoxicity (Minn et al., 2005), and overexpression of the gene sensitizes various cell types to oxidative stress with concomitant induction of apoptosis (World et al., 2006).

Loss of TXNIP due to a spontaneous nonsense mutation in HcB-19 mice results in 3-fold higher insulin levels in the fasted state, due principally to uncontrolled insulin secretion (Oka et al., 2006). These mice also display hypoglycemia, severe dyslipidemia, hyperketonemia, and liver steatosis. Genetic ablation of the gene in *txnip*$^{-/-}$ mice produces a nearly identical phenotype (Hui et al., 2004). In both mouse models, the TXNIP null background is accompanied by a metabolic block in gluconeogenesis, corresponding increases in the ratio of reduced:oxidized glutathione in liver, and a suspected impairment in TCA cycle activity. In wild-type mice, fasting causes a robust induction of TXNIP in the liver, consistent with TXNIP's presumed role in promoting gluconeogenesis and suggesting that the gene can be upregulated by metabolic cues other than hyperglycemia (Hui et al., 2004).

The new finding that TXNIP modulates glucose transport in skeletal muscle fits with the concept that muscle glucose uptake is governed by cellular energy state; for example, exercise enhances both basal and insulin-stimulated glucose uptake. Signals of energy deficiency such as accumulation of 5′AMP and resultant activation of 5′AMP-activated kinase play an established role in stimulating muscle glucose uptake in response to ATP depletion. Conversely, mounting clues hint toward a counteracting "signal of plenty" that puts the brakes on glucose transport when energy reserves are replete (Muoio and Newgard, 2006). In this way, sedentary muscles flooded with fuel in the form of sugar, lipid, and/or protein are discouraged from importing additional energy sources. Although the molecular nature of this signal remains a mystery, prominent candidates include specific lipid-derived intermediates, which would play a direct role in blocking insulin signaling (Morino et al., 2006). Conceivably, however, the message to abort glucose uptake might instead (or additionally) stem from changes in redox potential, as reflected by adjustments in NAD(P)H/NAD(P) and associated regulatory circuits involving

glutathione and thioredoxin. Attractively, this scenario could explain glucose intolerance provoked by oversupply of any metabolic substrate.

Because TXNIP plays a known role in regulating both redox state and oxidative stress, the new findings also have relevance for an emergent theory linking insulin resistance to dysfunctional mitochondria—a potential source and target of reactive oxygen species (ROS) (Muoio and Newgard, 2006; Morino et al., 2006). Fluctuations in redox state impact production of and defense against ROS, which are increasingly recognized as bona fide signaling molecules that can affect metabolic control. Interestingly, TXNIP is present in mitochondria and has been shown to bind the mitochondrially localized isoform of thioredoxin (Oka et al., 2006), although the biological relevance of this interaction remains unknown. While our understanding of how oxidative stress fits into the etiology of diabetes remains incomplete, a recent study found that ROS oppose glucose uptake and insulin signaling in cultured adipocytes (Houstis et al., 2006). TXNIP-mediated impairments in glucose transport might therefore reflect heightened oxidative stress. This exciting possibility now warrants further investigation.

Lastly, the report by Parikh et al. (2007) builds on evidence that pancreatic β cells and skeletal myocytes share common mechanisms of fuel sensing that ultimately cooperate to maintain whole-body glucose homeostasis (Muoio and Newgard, 2006). Whereas the islet responds by mobilizing insulin-containing vesicles, the muscle responds by modulating translocation of the resident glucose transporters. The recent findings implicate TXNIP as a diabetogenic culprit that disrupts both processes. Future research to gain a more mechanistic understanding of how TXNIP modulates glucose control might therefore lead to new therapeutic shelter from the current stormy climate.

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